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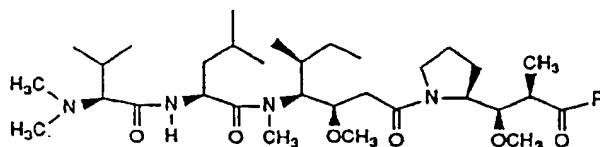
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(54) Human cancer inhibitory peptide amides

(57) This application discloses seven newly synthesized pentapeptide amides and four tetrapeptide amides. The synthesis utilized both naturally occurring and modified amino acids; the modified amino acids are constituents of the well known dolastatin 10 and dolastatin 15 which are structurally distinct peptides with excellent antineoplastic activity. These peptides were constructed by introducing a peptide bond between selected amino acids and modified amino acids and coupling the resulting di- and tri-peptides to obtain peptides having a high anticancer activity against a series of human cancer cell lines.



- | | |
|---------------------|-------------------|
| 8a) R= Met-NH-2ClPh | 8g) R= Met-NH-Q |
| 8b) R= Met-NH-4ClPh | 10a) R= Doe |
| 8c) R= Phe-NH-3ClPh | 10b) R= NH-2ClPEA |
| 8d) R= Phe-NH-4ClPh | 10c) R= NH-3ClPEA |
| 8e) R= Met-NH-BnThz | 10d) R= NH-4ClPEA |
| 8f) R= Pro-NH-BnThz | |

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Description

This invention relates generally to the field of cancer chemotherapy and more particularly to the synthesis of unique pentapeptide amides and tetra-peptide amide derivatives of dolastatin 10 which may be useful in chemotherapy.

Ancient marine invertebrate species of the Phyla Bryozoa, Molluska, and Porifera have been well established in the oceans for over one billion years. Such organisms have undergone trillions of biosynthetic reactions of their evolutionary chemistry to reach their present level of cellular organization, regulation and defense.

For example, marine sponges have changed minimally in physical appearance for nearly 500 million years. This suggests a very effective chemical resistance to evolution in response to changing environmental conditions over that period of time. Recognition of the potential for utilizing this biologically potent marine animal for medicinal purposes was recorded in Egypt about 2,700 B.C. and by 200 B.C. certain sea hare extracts were being used in Greece for their curative affect. This consideration along with the observation that marine animals, e.g. invertebrates and sharks, rarely develop cancer led to the systematic investigation of marine animal and plant anticancer compounds.

By 1968, ample evidence had been obtained, based on the U.S. National Cancer Institute's (NCI) key experimental cancer study systems, that certain marine organisms could provide new and antineoplastic and/or cytotoxic agents useful in chemotherapy and might also lead to compounds which would be effective in the control and/or eradication of viral diseases.

Further, these marine organisms were believed to possess potentially useful drug candidates of unprecedented structure which had eluded discovery by other methods of medicinal chemistry. Fortunately, these expectations have been realized, e.g. the discovery of the bryostatins, dolastatins and cephalostatins, many of which are now in preclinical development or human clinical studies.

Those researchers presently involved in medicinal chemistry know well the time lag between the isolation of a new compound and its introduction to the market. Often this procedure takes several years and may take decades. As a result, industry, in association with the U.S. Government, has developed a system of testing criteria which serves two purposes. One is to eliminate those substances which are shown through testing to be economically counter-productive to pursue. The second, more important purpose serves to identify those compounds which demonstrate a high likelihood of success and therefore warrant the further study and qualification, and attendant expense, necessary to meet the stringent regulatory requirements which control the ultimate market place.

Current research in the control of cancer in the United States is coordinated by the National Cancer Institute (NCI). To determine whether a substance has anti-cancer properties, the NCI has established a systematic protocol. This protocol, which involves the testing of a substance against a standard cell line panel containing 60 human tumor cell lines, has been verified and is accepted in scientific circles. The protocol, and the established statistical means for analyzing the results obtained by the standardized testing are fully described in the literature. See: Boyd, Dr. Michael R., Principles & Practice of Oncology, PPO Updates, Volume 3, Number 10, October 1989, for an in depth description of the testing protocol; and Paull, K. D., "Display and Analysis of Patterns of Differential Activity of Drugs Against Human Tumor Cell Lines; Development of Mean Graph and COMPARE Algorithm", Journal of the National Cancer Institute Reports, Vol. 81, No. 14, Page 1088, July 14, 1989 for a description of the methods of statistical analysis. Both of these references are incorporated herein by this reference thereto.

Numerous substances have been discovered which demonstrate significant antineoplastic or tumor inhibiting characteristics. As stated above, many of these compounds have been extracted, albeit with great difficulty, from marine animals such as the sponge and sea hare. Once isolation and testing of these compounds has been accomplished, a practical question remains, namely how to produce commercially significant quantities of the desired substance.

Quinine, which is available in practical quantities from the bark of the cinchona plant, differs from the compounds which are extracts of marine creatures possessing antineoplastic qualities. The collection and processing of these later compounds from their natural sources ranges from grossly impractical to the utterly impossible. Ignoring the ecological impact, the population of these creatures and the cost of collection and extraction make the process unworkable. Artificial synthesis of the active compounds is the only possible solution.

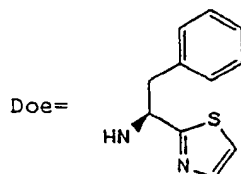
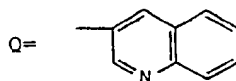
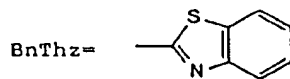
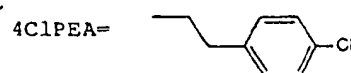
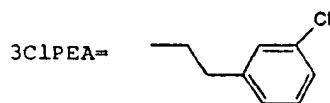
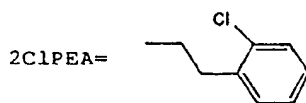
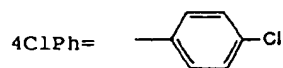
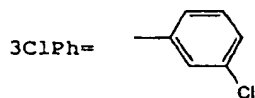
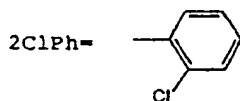
Therefore, the elucidation of the structure of these antineoplastic compounds is essential. After the structure has been determined, then a means of synthesis must be determined. This is often a long and arduous procedure due to the idiosyncratic complexity of these naturally occurring, evolutionary modified compounds. In addition, research is necessary to determine whether any portion of the naturally occurring compound is irrelevant to the desired properties, so that focus can be on the simplest structure having the perceived properties.

The investigation of potentially useful antineoplastic peptides offers one of the most promising approaches to new anticancer drugs. Continuing research along these lines has now resulted in the discovery and synthesis of seven new pentapeptide amides and four new tetrapeptide amides. In the syntheses of these peptides, naturally occurring as well as some modified amino acids have been utilized. The modified amino acids disclosed herein are constituents of the well known dolastatin 10 and dolastatin 15 which are structurally distinct peptides with excellent antineoplastic activity. Presently dolastatin 10 represents the most important member of the dolastatin family and is a potentially useful anti-

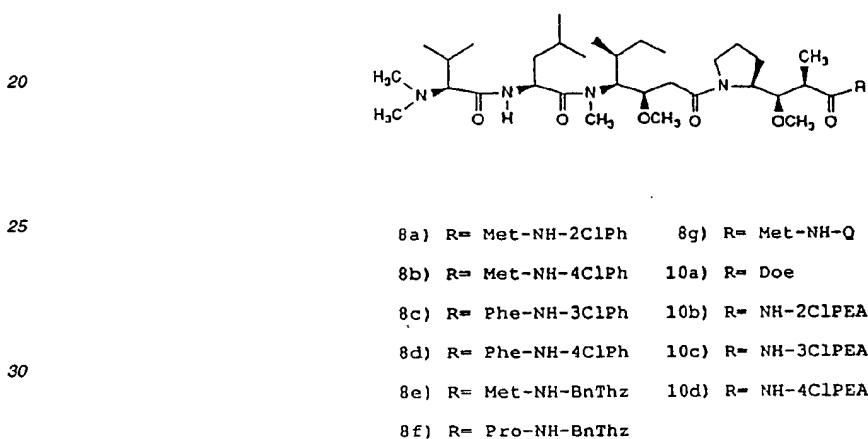
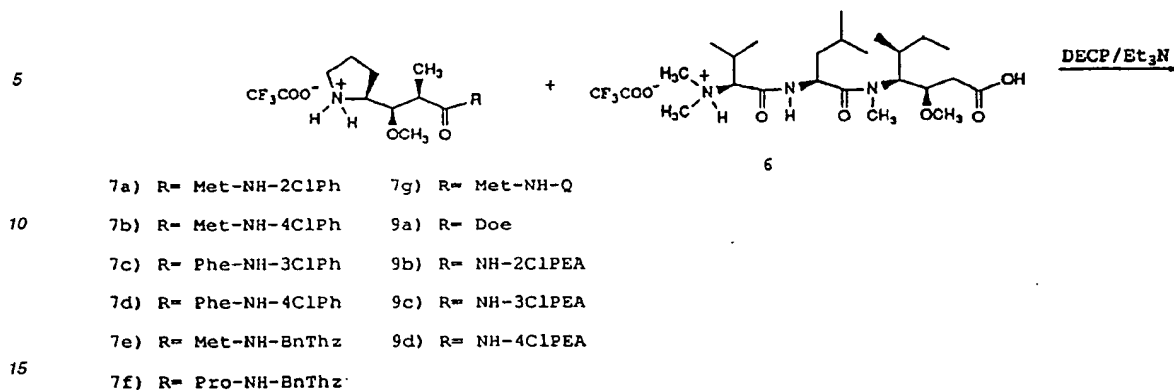
cancer drug. Herein disclosed are new compounds having excellent activity against a series of human cancer cell lines.

The novel peptides disclosed herein were constructed by introduction of a peptide bond between selected amino acids and modified amino acids and coupling the resulting di- and tri-peptides to obtain peptides having a very high anticancer activity. The research has led to the discovery and synthesis of new and very potent anticancer peptide amides. The present disclosure involves eleven such compounds: namely seven pentapeptide amides herein designated **8a-g** and four tetrapeptide amides herein designated **10a-d**.

The synthesis of these compounds was achieved in the following manner using the following terminology and abbreviations: the abbreviations are as follows:







35 The common tripeptide 5 needed for the synthesis of these peptides was synthesized starting from dolaisoleuine (Dil), a modified amino acid. Dolaisoleuine was coupled with N-cbz-(L)-Leucine (1) using bromotris (dimethylamino) phosphonium hexafluorophosphate (BrOP) as the coupling agent in presence of diisopropylethylamine to obtain the dipeptide N-Z-Leu-Dil-OBu^t (3). The N-carbobenzoyloxy protecting group of the dipeptide 3 was then removed with 5% Pd-C in cyclohexene to afford the free base which was coupled with dolavaline (Dov, a modified amino acid) with diethyl cyanophosphonate (DECP) as the coupling agent to give the required tripeptide Dov-Leu-Dil-OBu^t (5). The t-boc protecting group of the tripeptide (5) was then removed with trifluoro-acetic acid to obtain the trifluoroacetate salt (6).

40 The resulting tripeptide-tfa salt (6) was coupled with seven known dipeptide amide trifluoroacetate salts (7a-g) as well as four known dolaproine amide trifluoroacetate salts (9a-d) using DECP as the coupling agent to obtain the respective pentapeptide amides (8a-g) and tetrapeptide amides (10a-d) in good yields

45 All these compounds demonstrated excellent growth inhibition when administered to a variety of human cancer and mouse leukemia cell lines. The biological results are disclosed in Tables 1 and 2 below.

Accordingly, the primary object of the subject invention is the synthesis of peptide derivatives of dolastatin 10, which demonstrates extraordinary inhibition of cell growth and/or anti-cancer activity at substantially reduced cost.

Another object of the present invention is to identify the active portions of dolastatin 10 derivatives which can be attached to other molecules to provide an equally effective but considerably less expensive tumor inhibiting agents.

50 These and still further objects as shall hereinafter appear are readily fulfilled by the present invention in a remarkably unexpected manner as will be readily discerned from the following detailed description of exemplary embodiments thereof.

In vitro testing is an absolutely essential factor in the ongoing venture to discover new compounds for use in fighting the scourge of cancer. Without such screening, the process of obtaining new candidate drugs would be even more complex and expensive, if not impossible. To understand this process, and recognize the outstanding results demonstrated by some of the compositions disclosed herein, one must first understand the procedures, the nomenclature, and the data analysis involved. A brief description of the appropriate terminology follows:

ED₅₀ (P388) and GI₅₀ (HTCL) identify the drug dose which reduces the percent tumor/cell growth to 50%. There

is no mathematical difference between ED_{50} and GI_{50} , both of which are calculated using the same formula. The only difference is historical usage.

TGI, means "Total Growth Inhibition", and identifies the drug dose needed to yield zero percent growth, i.e. there are just as many cells at the end of the experiment as were present at the beginning. Whether just as many cells were killed as were produced (steady state), or no growth occurred (total inhibition) cannot be distinguished.

LC₅₀, means "Lethal Concentration 50%", and identifies the drug concentration which reduces to one-half of the cells originally present at the beginning of the experiment.

Each drug is tested at five (5) doses: 100 - 10 - 1 - 0.1 - 0.01 - $\mu\text{g/mL}$. Percent Growths are calculated for each dose. The two (or three) doses with growth values above, below, (or near to) 50% growth are used to calculate the ED_{50}/GI_{50} values using a linear regression computation. If no dose yields a growth value under 50%, the results are expressed as: $ED_{50} > (\text{highest dose})$. If no dose yields growth higher than 50% growth, then $ED_{50} < (\text{lowest dose})$. Similar calculations are performed for the TGI at 0% growth, and at -50% growth for the LC_{50} .

At the start of each experiment, cells from the in vitro cell cultures are inoculated into the appropriate tubes or microtiter plates. One set of control tubes/plates is immediately counted to determine the number of cells at the start of the experiment. This is the "baseline count", or "Tzero reading". At the end of the experiment (48 hrs later), a second set of control tubes/plates is analyzed to determine the "Control Growth" value. The growth (or death) of cells relative to the initial quantity of cells is used to define the "Percent of Growth."

EXAMPLE:

Baseline Count 20
Control Count 200
(10-Fold Growth)

100% Growth=Control Growth	100% Growth = 200
50% Growth= $T_{\text{zero}} + \frac{\text{Control} - T_{\text{zero}}}{2}$	50% Growth = 110
0% Growth = T_{zero}	0% Growth = 20
-50% Growth = $T_{\text{zero}} / 2$	-50% Growth = 10

Now that the relevant definitions and data analysis techniques have been disclosed, this disclosure can now turn to the particular compounds disclosed herein.

The synthesis of potentially useful peptides presents one of the most essential and promising approaches to new types of anticancer and immunosuppressant drugs. The Dolastatins, an unprecedented series of linear and cyclic antineoplastic and/or cytostatic peptides isolated from Indian Ocean sea hare *Dolabella auricularia* represent excellent leads for synthetic modification. The very productive sea hare *Dolabella auricularia* has produced a number of structurally distinct peptides with excellent antineoplastic activity. Presently Dolastatin 10, a linear pentapeptide, represents the most important member and is a potentially useful antineoplastic agent. Dolastatin 10 shows one of the best antineoplastic activity profiles against various cancer screens presently known. Recently the total synthesis and absolute configuration of this structurally unique and biologically active peptide was discovered. This compound has been tested in vivo and demonstrated significant activity, as shown below.

Experimental Anticancer Activity of Dolastatin 10 in
Murine in vivo Systems, T/C ($\mu\text{g/kg}$)

5	<u>P388 Lymphocytic Leukemia</u>	LOX Human Melanoma Xenograph (Nude Mouse)
	toxic (13.0)	toxic (52)
	155 and 17% cures (6.5)	301 and 67% cures (26)
10	146 and 17% cures (3.25)	301 and 50% cures (13)
	137 (1.63)	206 and 33% cures (6.5)
		170 and 17% cures (3.25)
15	<u>L1210 Lymphocytic Leukemia</u>	LOX in separate experiments
	152 (13)	340 and 50% cures (43)
	135 (6.5)	181 and 33% cures (26)
	139 (3.25)	192 (15)
20	120 (1.63)	138 and 17% cures (9.0)
	<u>B16 Melanoma</u>	Human Mammary Xenograph Nude Mouse
	238 and 40% cures (11.11)	Toxic (26)
25	182 (6.67)	137 (13)
	205 (4.0)	178 (6.25)
	171 (3.4)	
	142 (1.44)	
30	<u>M5076 Ovary Sarcoma</u>	OVCAR-3 Human Ovary Xenograph Nude Mouse
	toxic (26)	300 (40)
	166 (13)	
	142 (6.5)	
	151 (3.25)	
35		MX-1 Human Mammary Xenograft (Tumor Regression)
		14 (52)
		50 (26)
		61 (13)
40		69 (6.25)

Dolastatin 10 has also been tested against a minipanel from the NCI Primary screen. These results appear below, showing the amount of Dolastatin 10 required to attain GI_{50} in $\mu\text{g/ml}$, against the cell lines set forth below.

45	<u>OVCAR-3</u> (A)	<u>SF 295</u> (B)	<u>A498</u> (C)	<u>NCI-H460</u> (D)
	9.5×10^{-7}	7.6×10^{-8}	2.6×10^{-5}	3.4×10^{-6}
50	<u>KM20L2</u> (E)	<u>SK-MEL-5</u> (F)		
	4.7×10^{-6}	7.4×10^{-6}		

Similarly, the compounds disclosed herein have also been tested against an NCI in vitro mini panel. For each of six cell lines GI_{50} , TGI, and LC_{50} amounts were calculated for each compound. Each compound was also tested against the PS-388 cell line and for this test an ED_{50} was calculated.

55 The protocols followed, for the NCI minipanel are, except for the number of cell lines, those established by M.R. Boyd Ph.D., and well known to those of ordinary skill in the art. The procedure followed for the test against PS-388 Leukemia is the same that was followed in the superseded NCI P-388 screening test, which is also well known to those having ordinary skill in the art.

Table 1. Human Cancer-Cell line and PS-388 Mouse Leukemia (ED₅₀)
data for the pentapeptide amides 8a-g

	Cell type	Cell line	8 a	8 b	8 c	8 d
GI-50 (µg/ml)	Ovarian	OVCAR-3	0.00047	0.000031	0.000064	0.0000085
	CNS	SF-295	0.0034	0.0029	0.00088	0.00034
	Renal	A 498	0.0037	0.00045	0.00042	0.00018
	Lung-NSC	NCI-H460	0.0028	0.003	0.0017	0.00032
	Colon	KM20L2	0.0018	0.00028	0.00021	0.000015
	Melanoma	SK-MEL-5	0.042	0.000018	0.000042	0.0000051
TGI (µg/ml)	Ovarian	OVCAR-3	0.005	0.0016	0.0011	0.00023
	CNS	SF-295	>0.01	>0.01	>0.01	>0.01
	Renal	A 498	>0.01	>0.01	>0.01	0.0038
	Lung-NSC	NCI-H460	0.0079	0.009	0.0054	0.0011
	Colon	KM20L2	>0.01	>0.01	0.0012	0.0012
	Melanoma	SK-MEL-5	>0.01	>0.01	0.00074	>0.01
LC-50 (µg/ml)	Ovarian	OVCAR-3	>0.01	>0.01	>0.01	>0.01
	CNS	SF-295	>0.01	>0.01	>0.01	>0.01
	Renal	A 498	>0.01	>0.01	>0.01	>0.01
	Lung-NSC	NCI-H460	>0.01	>0.01	>0.01	>0.01
	Colon	KM20L2	>0.01	>0.01	>0.01	>0.01
	Melanoma	SK-MEL-5	>0.01	>0.01	>0.01	>0.01
ED-50 (µg/ml)	Mouse Leukemia	PS-388	0.00256	0.000434	0.0000371	0.0000025

	Cell type	Cell line	8 e	8 f	8 g
GI-50 (µg/ml)	Ovarian	OVCAR-3	0.00008	0.0033	<0.000006
	CNS	SF-295	0.0036	>0.01	0.00041
	Renal	A 498	0.00087	>0.01	0.00026
	Lung-NSC	NCI-H460	0.0032	>0.01	0.00032
	Colon	KM20L2	0.00034	0.0074	0.000019
	Melanoma	SK-MEL-5	0.000051	0.0043	<0.000006
TGI (µg/ml)	Ovarian	OVCAR-3	0.0029	>0.01	0.001
	CNS	SF-295	>0.01	>0.01	>0.01
	Renal	A 498	>0.01	>0.01	>0.01
	Lung-NSC	NCI-H460	>0.01	>0.01	0.0012
	Colon	KM20L2	>0.01	>0.01	0.0012
	Melanoma	SK-MEL-5	>0.01	>0.01	>0.01
LC-50 (µg/ml)	Ovarian	OVCAR-3	>0.01	>0.01	>0.01
	CNS	SF-295	>0.01	>0.01	>0.01
	Renal	A 498	>0.01	>0.01	>0.01
	Lung-NSC	NCI-H460	>0.01	>0.01	>0.01
	Colon	KM20L2	>0.01	>0.01	>0.01
	Melanoma	SK-MEL-5	>0.01	>0.01	>0.01
ED-50 (µg/ml)	Mouse Leukemia	PS-388	0.000839	0.00405	0.000271

Table 2.

Human Cancer-Cell line and PS-388 Mouse Leukemia (ED ₅₀) data for the tetrapeptide amides 10a-d						
	Cell type	Cell line	10a	10b	10c	10d
GI-50 (μg/ml)	Ovarian	OVCAR-3	0.000031	0.00031	0.0019	0.00029
	CNS	SF-295	0.00027	0.00042	0.0035	0.0017
	Renal	A498	0.00026	0.00069	0.0038	0.0059
	Lung-NSC	NCI-H460	0.00022	0.00033	0.0029	0.0024
	Colon	KM20L2	0.000034	0.00031	0.0020	0.00011
	Melanoma	SK-MEL-5	0.000058	0.00043	0.0025	0.00091
TGI (μg/ml)	Ovarian	OVCAR-3	0.00051	0.0012	>0.01	0.012
	CNS	SF-295	>0.01	>0.01	>0.01	0.1
	Renal	A498	0.0063	>0.01	>0.01	0.29
	Lung-NSC	NCI-H460	0.0007	0.0014	0.0084	0.0097
	Colon	KM20L2	0.001	0.0013	>0.01	0.011
	Melanoma	SK-MEL-5	>0.01	>0.01	>0.01	>1
LC-50 (μg/ml)	Ovarian	OVCAR-3	>0.01	>0.01	>0.01	>1
	CNS	SF-295	>0.01	>0.01	>0.01	>1
	Renal	A498	>0.01	>0.01	>0.01	>1
	Lung-NSC	NCI-H460	>0.01	>0.01	>0.01	>1
	Colon	KM20L2	>0.01	>0.01	>0.01	>1
	Melanoma	SK-MEL-5	>0.01	>0.01	>0.01	>1
ED-50 (μg/ml)	Mouse Leukemia	PS-388	0.0000312	0.000357	0.00314	0.00586

The compound identified by reference (3) N-Z-Leu-Dil-OBu¹ was prepared in the following manner, following what is identified below as General Procedure A.

General Procedure A

To a solution of the hydrochloride salt of Dolaisoleuine t-butyl ester(2, 4.39 mM) and N-Z-(L)-Leucine (1, 4.83 mM) in dry dichloromethane(15 mL), cooled to ice-bath temperature (0-5° C) was added diisopropylethylamine(14.49 mM) followed by BrOP(4.83 mM) and the resulting solution was stirred at the same temperature for 2 hours. The solvents were removed under reduced pressure and the residue was chromatographed on a SILICA GEL column using 1:4 acetone-hexane as the solvent to obtain the required dipeptide as an oily substance (3, 72%); R_f 0.53 (1:4 acetone-hexane); [α]_D²⁵ - 33.4° (c 6.2, CH₃OH); IR(neat): 2961, 1723, 1640, 1528, 1456, 1368, 1254, 1154 and 1101 cm⁻¹; ¹H NMR (CDCl₃, 300MHZ): 7.32(m, 5H, ArH), 5.47 (d, J= 8.9Hz, 1H, NH), 5.08(s, 2H, ArCH₂), 4.68(m, 1H, dil N-CH), 4.55(m, 1H, Leu C^α H), 3.87(m, 1H, CH-OMe), 3.32(s, 3H, OMe), 2.92(s, 3H, N-Me), 2.26-2.46(m, 2H, CH₂CO), 1.30-1.70(m, 6H, 2 x CH₂, 2 x CH), 1.44, 1.43(s, 9H, t-Bu) and 0.80-1.04(m, 12H, 4 x CH₃); EIMS (m/z): 506(M⁺), 348, 279, 220, 177, 128, 100(100%) and 91.

The compound identified by reference (5) Dov-Leu-Dil-OBu¹ was prepared in the following manner, following what is identified below as General Procedure B.

General Procedure B

A solution of Z-Leu-Dil-OBu¹ (3, 2.22 mM) was dissolved in anhydrous methanol (10 mL) and cyclohexene (10 mL) was added in a nitrogen atmosphere. To the solution was added 5% Pd-C (1.15g) and the mixture was heated at reflux for 6 minutes. The catalyst was removed by filtering through a layer of celite, the solvent removed under reduced pressure, and the residue dried in high vacuum for 2 hours.

To a solution of the above free base and N,N-dimethyl-(L)-valine(4, 2.66 mM) in dry dichloromethane (10 mL) was added triethylamine (2.66 mM) followed by DECP (2.66 mM) at 0-5 °C under argon atmosphere. After stirring at the same temperature for 2 hours, the solvent was removed and the residue chromatographed on a SILICA GEL column with 15% acetone in hexane as solvent to give the required tripeptide t-butyl ester as a colorless gummy mass (5, 65%);

R_f 0.69 (30% acetone-hexane); $[\alpha]_D^{25}$ -24.8° (c 5.0, CH₃OH); IR(neat): 2961, 1730, 1626, 1524, 1452, 1368, 1294, 1154 and 1101 cm⁻¹; ¹H NMR(CDCl₃, 300MHz): 6.82(br d, J = 8.8Hz, 1H, NH), 5.01(m, 1H, dil CHN), 4.60(br m, 1H, Leu C α -H), 3.85(m, 1H, CH-OMe), 3.33(s, 3H, OMe), 2.97(s, 3H, dil N-Me), 2.2-2.5(m, 2H, CH₂-CO), 2.24(s, 6H, NMe₂), 2.05(m, 1H, dov C α -H), 1.2-1.8(m, 7H, 2x CH₂, 3 x CH), 1.42, 1.44(s, 9H, *t*-Bu) and 0.75-0.99(m, 18H, 6 x CH₃); EIMS (m/z): 499(M⁺), 456, 241, 186, 101, and 100(100%).

The tripeptide trifluoroacetate salt, identified above by reference (6) was synthesized following what is identified below as General Procedure C.

General Procedure C

To a solution of the tripeptide *t*-butyl ester(5, 10 mM) in dichloromethane(10 mL) cooled to ice-bath temperature was added trifluoroacetic acid(10 mL) under argon atmosphere and the solution was stirred at the same temperature for 1 hour. The solvents were then removed under reduced pressure, the residue was dissolved in toluene and solvent again removed under reduced pressure. The residue was dried *in vacuo* and crystallized from diethyl ether to obtain the tripeptide trifluoroacetate salt(6, quantitative) as a colorless solid; M.p. 168-169 °C; $[\alpha]_D^{25}$ -36° (c 0.1, CHCl₃); IR (thin film): 2938, 2880, 2834, 1672, 1632, 1549, 1485, 1466, 1416, 1385, 1317, 1296, 1240, 1201, 1181, 1136, 1099, 1009, 990, 833, 799, 737, 721 and 617 cm⁻¹.

The pentapeptide amides herein identified by references 8a-g and 10a-d, were synthesized following General Procedure D shown below;

General Procedure D

To a solution of the trifluoroacetate salt (7a-g, 9a-d, 0.2 mM) in methylene chloride (2 mL, distilled from calcium hydride) was added the Dov-Leu-Dil tripeptide trifluoroacetate salt (6, 0.2 mM) followed by triethylamine (0.63 mM) and DECP (0.22 mM, ice bath). The solution was stirred under argon at 0-5°C for 1-2 hours. The solvent was removed (under vacuum at room temperature) and the residue was chromatographed on a SILICA GEL (0.040-0.063 mm) column. After the evaporation of solvent from the fractions (selected by thin layer chromatography) the required peptide amides were obtained as a fluffy solid.

Chromatography over SILICA GEL with hexane-acetone (2:3) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Methionine N-2-chlorophenylamide (8a) as a white solid (C₄₃H₇₃N₆O₇S₁Cl₁, 81%); R_f 0.26 (hexane-acetone 1:1); M. p. 88-90 °C; $[\alpha]_D^{23}$ = -57.6° (c 0.17, CHCl₃); IR (thin film): 3293, 2963, 2932, 2876, 1628, 1593, 1532, 1441, 1385, 1370, 1294, 1269, 1233, 1200, 1165, 1134, 1099, 1051 and 752 cm⁻¹; EIMS (70eV) m/z : 852 (M⁺).

Chromatography over SILICA GEL with hexane-acetone (1:1) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Methionine N-4-chlorophenylamide (8b) (C₄₃H₇₃N₆O₇S₁Cl₁, 98%); R_f 0.32 (hexane-acetone 1:1); M. p. 95-96 °C; $[\alpha]_D^{23}$ = -64.4° (c 0.09, CHCl₃); IR (thin film): 3306, 3293, 2961, 2934, 2874, 1643, 1626, 1543, 1493, 1449, 1418, 1404, 1385, 1368, 1304, 1289, 1269, 1250, 1198, 1169, 1134, 1098, 1038 and 829 cm⁻¹; EIMS (70eV) m/z : 852 (M⁺).

Chromatography over SILICA GEL with hexane-acetone (1:1) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Phenylalanine N-3-chlorophenylamide (8c) (C₄₇H₇₃N₆O₇Cl₁, 99%); R_f 0.34 (hexane-acetone 1:3); M. p. 86-88 °C; $[\alpha]_D^{23}$ = -47.8° (c 0.18, CHCl₃); IR (thin film): 3306, 3293, 2963, 2934, 2876, 2832, 1649, 1626, 1595, 1545, 1483, 1452, 1425, 1385, 1368, 1302, 1267, 1250, 1236, 1194, 1167, 1134, 1099, 1038, 978, 779 and 741 cm⁻¹; EIMS (70eV) m/z : 868 (M⁺).

Chromatography over SILICA GEL with hexane-acetone (2:3) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Phenylalanine N-4-chlorophenylamide (8d) as a glassy solid (C₄₇H₇₃N₆O₇Cl₁, 82%); R_f 0.33 (hexane-acetone 1:1); M. p. 88-90 °C; $[\alpha]_D^{23}$ = -54.3° (c 0.14, CHCl₃); IR (thin film): 3306, 3295, 2961, 2932, 2874, 1649, 1626, 1543, 1493, 1454, 1418, 1404, 1385, 1368, 1306, 1290, 1269, 1248, 1200, 1134, 1098, 1038, 1015 and 829 cm⁻¹; EIMS (70eV) m/z : 868 (M⁺).

Chromatography over SILICA GEL with acetone-hexane (3:2) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Methionine N-2-benzothiazolamide (8e) (C₄₄H₇₃N₇O₇S₂, 93%); R_f 0.27 (hexane-acetone 1:1); $[\alpha]_D^{25}$ = -49.2° (c 0.13, CHCl₃); M. p. 90-92 °C; IR (thin film): 3306, 3293, 3214, 3196, 2961, 2932, 2874, 1626, 1547, 1443, 1420, 1387, 1368, 1263, 1235, 1194, 1165, 1099, 1036 and 756 cm⁻¹; EIMS m/z : 875 (M⁺).

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Proline N-2-benzothiazolamide (8f) (C₄₄H₇₁N₇O₇S, 60%); R_f 0.20 (hexane-acetone 1:1); $[\alpha]_D^{25}$ = -39.1° (c 0.11, CHCl₃); M. p. 96-99 °C; IR (thin film): 3306, 2961, 2932, 2876, 1703, 1626, 1549, 1443, 1385, 1263, 1169 and 1098 cm⁻¹; EIMS m/z : 842 (M⁺).

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded

L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuin yl-(2R,3R, 4S)-Dolaproinyl-L-Methionine N-3-quinolinamide (8g) as a glassy solid (C₄₆H₇₅N₇O₇S, 83%); R_f 0.14 (hexane-acetone 1:1); [α]_D²⁵ = -46.9° (c 0.16, CHCl₃); M. p. 118-120 °C; IR (thin film) ν : 3291, 2963, 2934, 2876, 1649, 1632, 1580, 1555, 1489, 1452, 1422, 1385, 1368, 1346, 1304, 1283, 1271, 1202, 1181, 1134, 1099, 1042, 785, 754, 719 and 615 cm⁻¹; EIMS m/z: 869 (M⁺).

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuinyl-(2R,3R,4S)-Dolaproinyl-Dolaphenine (10a) as a glassy solid (C₄₃H₇₀N₆O₆S, 84%); M.p. 77-78 °C; R_f 0.2 (acetone-hexane 1:1); [α]_D²⁵ = -68.6° (c 0.14, CHCl₃); IR (thin film): 3295, 2960, 2934, 2876, 2830, 1624, 1535, 1497, 1454, 1418, 1385, 1370, 1319, 12287, 1267, 1225, 1200, 1171, 1136, 1101, 1040, 735, 698, 619, 610 and 536 cm⁻¹; EIMS (m/z): 798 (M⁺).

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuinyl-(2R,3R,4S)-Dolaproinyl-N-2(2-chlorophenyl) ethylamide (10b) as a gummy mass (C₄₀H₆₈N₅O₆Cl₁, 77%); R_f 0.27 (acetone-hexane 1:1); [α]_D²⁵ = -54.3° (c 0.07, CHCl₃); IR (thin film): 3308, 2961, 2934, 2876, 2830, 1624, 1537, 1451, 1418, 1383, 1366, 1287, 1269, 1223, 1198, 1169, 1157, 1134, 1101, 1055, 1040 and 754 cm⁻¹; EIMS (m/z): 749 (M⁺).

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuin yl-(2R,3R,4S)-Dolaproinyl-N-2(3-chlorophenyl) ethylamide (10c) as a gummy mass (C₄₀H₆₈N₅O₆Cl₁, 75%); R_f 0.23 (acetone-hexane 1:1); [α]_D²⁵ = -47.8° (c 0.09, CHCl₃); IR (thin film): 3308, 2961, 2934, 2876, 2830, 1643, 1624, 1537, 1452, 1418, 1383, 1366, 1289, 1267, 1223, 1200, 1169, 1136, 1101, 1039, 781 and 685 cm⁻¹; EIMS (m/z): 749 (M⁺).

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuinyl -(2R,3R,4S)-Dolaproinyl-N-2(4-chlorophenyl) ethylamide (10d) as a glassy solid (C₄₀H₆₈N₅O₆Cl₁, 79%); R_f 0.54 (acetone-hexane 3:1); M.p. 67-70 °C; [α]_D²⁵ = -72.2° (c 0.09, CHCl₃); IR (thin film): 3308, 2961, 2934, 2876, 1624, 1541, 1493, 1451, 1418, 1385, 1366, 1269, 1225, 1198, 1136, 1099 and 1040 cm⁻¹; EIMS (m/z): 749 (M⁺).

To further aid in the understanding of the present invention, and not by way of limitation the following examples are presented.

EXAMPLE I

N-Z-Leu-Dil-OBu^t(3) was prepared as follows: To a solution of the hydrochloride salt of Dolaisoleuine t-butyl ester (2, 4.39 mM) and N-Z-(L)-Leucine (1, 4.83 mM) in dry dichloromethane (15 mL), cooled to ice-bath temperature (0-5 °C) was added diisopropylethylamine (14.49 mM) followed by BrOP (4.83 mM) and the resulting solution was stirred at the same temperature for 2 hours. The solvents were removed under reduced pressure and the residue was chromatographed on a SILICA GEL column using 1:4 acetone-hexane as the solvent to obtain the required dipeptide as an oily substance (3, 72%); R_f 0.53 (1:4 acetone-hexane); [α]_D²⁵ = -33.4° (c 6.2, CH₃OH); IR (neat): 2961, 1723, 1640, 1528, 1456, 1368, 1254, 1154 and 1101 cm⁻¹; ¹H NMR (CDCl₃, 300MHz): 7.32(m, 5H, ArH), 5.47 (d, J = 8.9Hz, 1H, NH), 5.08 (s, 2H, ArCH₂), 4.68(m, 1H, dil N-CH), 4.55(m, 1H, Leu C α H), 3.87(m, 1H, CH-OMe), 3.32(s, 3H, OMe), 2.92(s, 3H, N-Me), 2.26-2.46(m, 2H, CH₂CO), 1.30-1.70(m, 6H, 2 x CH₂, 2 x CH), 1.44, 1.43(s, 9H, t-Bu) and 0.80-1.04(m, 12H, 4 x CH₃); EIMS (m/z): 506 (M⁺), 348, 279, 220, 177, 128, 100 (100%) and 91.

EXAMPLE II

Dov-Leu-Dil-OBu^t(5) was prepared as follows: A solution of Z-Leu-Dil-OBu^t(3, 2.22 mM) was dissolved in anhydrous methanol (10 mL) and cyclohexene (10 mL) was added in a nitrogen atmosphere. To the solution was added 5% Pd-C (1.15g) and the mixture was heated at reflux for 6 minutes. The catalyst was removed by filtering through a layer of celite, the solvent removed under reduced pressure, and the residue dried in high vacuum for 2 hours.

To a solution of the above free base and N,N-dimethyl-(L)-valine(4, 2.66 mM) in dry dichloromethane (10 mL) was added triethylamine (2.66 mM) followed by DECP (2.66 mM) at 0-5 °C under argon atmosphere. After stirring at the same temperature for 2 hours, the solvent was removed and the residue chromatographed on a SILICA GEL column with 15% acetone in hexane as solvent to give the required tripeptide t-butyl ester as a colorless gummy mass (5, 65%); R_f 0.69 (30% acetone-hexane); [α]_D²⁵ = -24.8° (c 5.0, CH₃OH); IR (neat): 2961, 1730, 1626, 1524, 1452, 1368, 1294, 1154 and 1101 cm⁻¹; ¹H NMR (CDCl₃, 300MHz): 6.82(br d, J = 8.8Hz, 1H, NH), 5.01(m, 1H, dil CHN), 4.60(br m, 1H, Leu C α -H), 3.85(m, 1H, CH-OMe), 3.33(s, 3H, OMe), 2.97(s, 3H, dil N-Me), 2.2-2.5(m, 2H, CH₂-CO), 2.24(s, 6H, NMe₂), 2.05(m, 1H, dov C α -H), 1.2-1.8(m, 7H, 2x CH₂, 3 x CH), 1.42, 1.44(s, 9H, t-Bu) and 0.75-0.99(m, 18H, 6 x CH₃); EIMS (m/z): 499 (M⁺), 456, 241, 186, 101, and 100 (100%).

EXAMPLE III

Tripeptide Trifluoroacetate Salt(6) was prepared as follows: To a solution of the tripeptide t-butyl ester(5, 10 mM) in dichloromethane(10 mL) cooled to ice-bath temperature was added trifluoroacetic acid(10 mL) under argon atmosphere and the solution was stirred at the same temperature for 1 hour. The solvents were then removed under reduced pressure, the residue was dissolved in toluene and solvent again removed under reduced pressure. The residue was dried in vacuo and crystallized from diethyl ether to obtain the tripeptide trifluoroacetate salt(6, quantitative) as a colorless solid; M.p. 168-169 °C; $[\alpha]_D^{25} = -36^\circ$ (c 0.1, CHCl₃); IR(thin film): 2938, 2880, 2834, 1672, 1632, 1549, 1485, 1466, 1416, 1385, 1317, 1296, 1240, 1201, 1181, 1136, 1099, 1009, 990, 833, 799, 737, 721 and 617 cm⁻¹.

EXAMPLE IV

Pentapeptide amides 8a-g, 10a-d were prepared as follows: To a solution of the trifluoroacetate salt (7a-g, 9a-d, 0.2 mM) in methylene chloride (2 mL, distilled from calcium hydride) was added the Dov-Leu-Dil tripeptide trifluoroacetate salt (6, 0.2 mM) followed by triethylamine (0.63 mM) and DECP (0.22 mM, ice bath). The solution was stirred under argon at 0-5°C for 1-2 hours. The solvent was removed (under vacuum at room temperature) and the residue was chromatographed on a SILICA GEL (0.040-0.063 mm) column. After the evaporation of solvent from the fractions (selected by thin layer chromatography), the required peptide amides were obtained as a fluffy solid.

EXAMPLE IV-a

Chromatography over SILICA GEL with hexane-acetone (2:3) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Methionine N-2-chlorophenylamide (8a) as a white solid (C₄₃H₇₃N₆O₇S₁Cl₁, 81%); Rf 0.26 (hexane-acetone 1:1); M. p. 88-90 °C; $[\alpha]_D^{23} = -57.6^\circ$ (c 0.17, CHCl₃); IR (thin film): 3293, 2963, 2932, 2876, 1628, 1593, 1532, 1441, 1385, 1370, 1294, 1269, 1233, 1200, 1165, 1134, 1099, 1051 and 752 cm⁻¹; EIMS (70eV) m/z: 852 (M⁺).

EXAMPLE IV-b

Chromatography over SILICA GEL with hexane-acetone (1:1) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Methionine N-4-chlorophenylamide (8b) (C₄₃H₇₃N₆O₇S₁Cl₁, 98%); Rf 0.32 (hexane-acetone 1:1); M. p. 95-96 °C; $[\alpha]_D^{23} = -64.4^\circ$ (c 0.09, CHCl₃); IR (thin film): 3306, 3293, 2961, 2934, 2874, 1643, 1626, 1543, 1493, 1449, 1418, 1404, 1385, 1368, 1304, 1289, 1269, 1250, 1198, 1169, 1134, 1098, 1038 and 829 cm⁻¹; EIMS (70eV) m/z: 852 (M⁺).

EXAMPLE IV-c

Chromatography over SILICA GEL with hexane-acetone (1:1) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Phenylalanine N-3-chlorophenylamide (8c) (C₄₇H₇₃N₆O₇Cl₁, 99%); Rf 0.34 (hexane-acetone 1:3); M. p. 86-88 °C; $[\alpha]_D^{23} = -47.8^\circ$ (c 0.18, CHCl₃); IR (thin film): 3306, 3293, 2963, 2934, 2876, 2832, 1649, 1626, 1595, 1545, 1483, 1452, 1425, 1385, 1368, 1302, 1267, 1250, 1236, 1194, 1167, 1134, 1099, 1038, 978, 779 and 741 cm⁻¹; EIMS (70eV) m/z: 868 (M⁺).

EXAMPLE IV-d

Chromatography over SILICA GEL with hexane-acetone (2:3) as eluent, according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Phenylalanine N-4-chlorophenylamide (8d) as a glassy solid (C₄₇H₇₃N₆O₇Cl₁, 82%); Rf 0.33 (hexane-acetone 1:1); M. p. 88-90 °C; $[\alpha]_D^{23} = -54.3^\circ$ (c 0.14, CHCl₃); IR (thin film): 3306, 3295, 2961, 2932, 2874, 1649, 1626, 1543, 1493, 1454, 1418, 1404, 1385, 1368, 1306, 1290, 1269, 1248, 1200, 1134, 1098, 1038, 1015 and 829 cm⁻¹; EIMS (70eV) m/z: 868 (M⁺).

EXAMPLE IV-e

Chromatography over SILICA GEL with acetone-hexane (3:2) as eluent according to General Procedure D, yielded L-Dolavalyl-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuyl-(2R,3R,4S)-Dolaproinyl-L-Methionine N-2-benzothiazolamide (8e) (C₄₄H₇₃N₇O₇S₂, 93%); Rf 0.27 (hexane-acetone 1:1); $[\alpha]_D^{25} = -49.2^\circ$ (c 0.13, CHCl₃); M. p. 90-92 °C; IR (thin film): 3306, 3293, 3214, 3196, 2961, 2932, 2874, 1626, 1547, 1443, 1420, 1387, 1368, 1263, 1235, 1194, 1165, 1099, 1036 and 756 cm⁻¹; EIMS m/z: 875 (M⁺).

EXAMPLE IV-f

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded L-Dolavaly-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuiny-(2R,3R,4S)-Dolaproiny-L-Proline N-2-benzothiazolamide (8f) ($C_{94}H_{71}N_7O_7S$, 60%); R_f 0.20 (hexane-acetone 1:1); $[\alpha]_D^{25} = -39.1^\circ$ (c 0.11, $CHCl_3$); M. p. 96-99 °C; IR (thin film): 3306, 2961, 2932, 2876, 1703, 1626, 1549, 1443, 1385, 1263, 1169 and 1098 cm^{-1} ; EIMS m/z : 842 (M^+).

EXAMPLE IV-g

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent according to General Procedure D, yielded L-Dolavaly-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuiny-(2R,3R,4S)-Dolaproiny-L-Methionine N-3-quinolinamide (8g) as a glassy solid ($C_{46}H_{75}N_7O_7S$, 83%); R_f 0.14 (hexane-acetone 1:1); $[\alpha]_D^{25} = -46.9^\circ$ (c 0.16, $CHCl_3$); M. p. 118-120 °C; IR (thin film): 3291, 2963, 2934, 2876, 1649, 1632, 1580, 1555, 1489, 1452, 1422, 1385, 1368, 1346, 1304, 1283, 1271, 1202, 1181, 1134, 1099, 1042, 785, 754, 719 and 615 cm^{-1} ; EIMS m/z : 869 (M^+).

EXAMPLE V-a

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded L-Dolavaly-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuiny-(2R,3R,4S)-Dolaproiny-Dolaphenine (10a) as a glassy solid ($C_{43}H_{70}N_6O_6S$, 84%); M.p. 77-78 °C; R_f 0.2 (acetone-hexane 1:1); $[\alpha]_D^{25} = -68.6^\circ$ (c 0.14, $CHCl_3$); IR (thin film): 3295, 2960, 2934, 2876, 2830, 1624, 1535, 1497, 1454, 1418, 1385, 1370, 1319, 12287, 1267, 1225, 1200, 1171, 1136, 1101, 1040, 735, and 698 cm^{-1} ; EIMS (m/z): 798(M^+).

EXAMPLE V-b

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent according to General Procedure D, yielded L-Dolavaly-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuiny-(2R,3R,4S)-Dolaproiny-N-2(2-chlorophenyl) ethylamide (10b) as a gummy mass ($C_{40}H_{68}N_5O_6Cl_1$, 77%); R_f 0.27 (acetone-hexane 1:1); $[\alpha]_D^{25} = -54.3^\circ$ (c 0.07, $CHCl_3$); IR (thin film): 3308, 2961, 2934, 2876, 2830, 1624, 1537, 1451, 1418, 1383, 1366, 1287, 1269, 1223, 1198, 1169, 1157, 1134, 1101, 1055, 1040 and 754 cm^{-1} ; EIMS (m/z): 749(M^+).

EXAMPLE V-c

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded L-Dolavaly-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuiny-(2R,3R,4S)-Dolaproiny-N-2(3-chlorophenyl) ethylamide (10c) as a gummy mass ($C_{40}H_{68}N_5O_6Cl_1$, 75%); R_f 0.23 (acetone-hexane 1:1); $[\alpha]_D^{25} = -47.8^\circ$ (c 0.09, $CHCl_3$); IR (thin film): 3308, 2961, 2934, 2876, 2830, 1643, 1624, 1537, 1452, 1418, 1383, 1366, 1289, 1267, 1223, 1200, 1169, 1136, 1101, 1039, 781 and 685 cm^{-1} ; EIMS (m/z): 749(M^+).

EXAMPLE V-d

Chromatography over SILICA GEL with acetone-hexane (3:1) as eluent, according to General Procedure D, yielded L-Dolavaly-L-Leucyl-N-methyl-(3R,4S,5S)-Dolaisoleuiny-(2R,3R,4S)-Dolaproiny-N-2(4-chlorophenyl) ethylamide (10d) as a glassy solid ($C_{40}H_{68}N_5O_6Cl_1$, 79%); R_f 0.54 (acetone-hexane 3:1); M.p. 67-70 °C; $[\alpha]_D^{25} = -72.2^\circ$ (c 0.09, $CHCl_3$); IR (thin film): 3308, 2961, 2934, 2876, 1624, 1541, 1493, 1451, 1418, 1385, 1366, 1269, 1225, 1198, 1136, 1099 and 1040 cm^{-1} ; EIMS (m/z): 749(M^+).

From the foregoing, it is readily apparent that a useful embodiment of the present invention has been herein described and illustrated which fulfills all of the aforesaid objectives in a remarkably unexpected fashion. It is of course understood that such modifications, alterations and adaptations as may readily occur to the artisan confronted with this disclosure are intended within the spirit of this disclosure which is limited only by the scope of the claims appended hereto.

Claims

1. A composition of matter having the general structure below:



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